Title: Natural oil-based emulsion containing allantoin versus aqueous cream for managing radiation-induced skin reactions in patients with cancer: a phase III double-blind randomised controlled trial

Running Title: Radiodermatitis topical intervention

Authors: Raymond Javan Chan^{*,†,††,†††}, R.N., B.N., M.AppSc.(Research), Ph.D., F.A.C.N.*

Jennifer Mann^{*}, R.N., B.N., Grad.Cert.HlthSc., Lee Tripcony^{*}, B.Sc., Jacqui Keller^{*}, B.Bus.(HIM), Robyn Cheuk^{*}, B.M.B.S., F.R.A.N.Z.C.R., Rae Blades^{*}, R.N., B.N., Grad.Cert.Nursing., Samantha Keogh^{†††}, R.N., Ph.D., Christopher Poole^{*††††}, B.Eng., M.Sc., Ph.D., Christopher Walsh^{*}, B.App.Sc.,

^{*}Cancer Care Services, Royal Brisbane & Women's Hospital, Butterfield Street, Herston, Q4029, Queensland, Australia

[†]School of Nursing, Queensland University of Technology, Kelvin Grove, Q4029, Australia.

^{††} Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, Q4029, Australia.

^{†††}NHMRC Centre for Research Excellence in Nursing, Centre for Health Practice Innovation - Griffith Health Institute, Griffith University, Nathan, Q4111, Australia

^{††††}Science and Engineering Faculty, Queensland University of Technology, Brisbane, Australia

Corresponding Author:

Raymond Chan

Address: Level 2, Bldg 34, Royal Brisbane and Women's Hospital, Herston, Q4029, Australia.

Telephone number: (617) 3646 5833

Fax number: (617) 3646 5832

Email: email.rchan@gmail.com

Conflicts of Interest:

This study received research grants and sponsorship from the Office of Medical and Health Research, Queensland Health, Cancer Nurses Society of Australia and the RBWH Foundation. The study also received financial support in the form of an unconditional donation and in-kind support through the supply of products for the study from Moogoo Skin Care. However, Moogoo Skin Care did not design the study protocol, collect or analyse data, and did not prepare the manuscript. None of the authors have any professional, consultancy, or commercial connection with the manufacturer. The authors have no financial interests to disclose.

ABSTRACT

Purpose: To investigate the effects of a natural oil-based emulsion containing allantoin versus aqueous cream for preventing and managing radiation induced skin reactions (RISR).

Methods and Materials: A total of 174 patients were randomised and participated in the study. Patients either received Cream 1 (the natural oil-based emulsion containing allantoin) or Cream 2 (aqueous cream). Skin toxicity, pain, itching and skin-related quality of life scores were collected for up to four weeks after radiation treatment.

Results: Patients who received Cream 1 had a significantly lower average level of Common Toxicity Criteria at week 3 ($p<0.05$), but had statistically higher average levels of skin toxicity at weeks 7, 8 and 9 (all $p<0.001$). Similar results were observed when skin toxicity was analysed by grades. With regards to pain, patients in the Cream 2 group had a significantly higher average level of worst pain ($p<0.05$) and itching ($p=0.046$) compared to the Cream 1 group at week 3, however these differences were not observed at other weeks. In addition, there was a strong trend for Cream 2 to reduce the incidence of grade 2 or more skin toxicity in comparison to Cream 1 ($p=0.056$). Overall, more participants in the Cream 1 group were required to use another topical treatment at weeks 8 ($p=0.049$) and 9 ($p=0.01$).

Conclusion: The natural oil-based emulsion containing allantoin appears to have similar effects for managing skin toxicity compared to aqueous cream up to week 5, however, it becomes significantly less effective at later weeks into the radiation treatment and beyond treatment completion (week 6 and beyond). There were no major differences in pain, itching and skin-related quality of life. In light of these results, clinicians and patients can base their decision on costs and preferences. Overall, aqueous cream appears to be a more preferred option.

INTRODUCTION

Radiotherapy remains an essential treatment for patients with cancer and is associated with a number of short term and long term side effects (1). One of these side effects includes radiation-induced skin reactions (RISR), also known as radiation dermatitis, which affects up to 90% of cancer patients receiving radiotherapy (2-4). The reactions are the combined result of a decrease in functional stem cells, changes in the skin's endothelial cells, inflammation, and skin cell necrosis (5). Radiation-induced skin reactions are often characterised by oedema, erythema, changes in pigmentation, fibrosis and ulceration (6, 7). Signs and symptoms may include skin dryness, itching discomfort, pain, warmth, and burning (7, 8). Radiation-induced skin reactions have an impact on pain and quality of life in this patient group (9), and if severe, may necessitate changes to the radiation schedule for the patient (10).

The development of RISR may begin immediately, with increasing toxicity occurring at 2-3 weeks, with effects accumulating across the course of treatment, and may persist up to 4 weeks after treatment ends (4). Risk factors influencing RISR could include age, general health, ethnic origin, co-existing diseases, ultraviolet exposure, hormonal status, genetic factors, treatment dose, volume, and number of fractions of radiation, radio-sensitizers, concurrent chemotherapy and the site of treatment (7, 11, 12). A range of interventions are used for prophylaxis and management of these reactions. These interventions include: (i) topical preparations (both steroidal and non-steroidal), (ii) dressings, (iii) systemic treatment such as amifostine, oral hydrolytic enzymes, pentoxifylline and zinc supplement, and (iv) alternating modes of radiation delivery. A recent overview of systematic reviews and a systematic review of randomised controlled trials conducted by our team concluded that the use of these interventions are not yet supported by conclusive evidence, and therefore warrant further investigations (10, 13).

Topical interventions are the most accessible form of treatment. A recently developed natural oil-based emulsion containing allantoin (NOCA) is an Australian owned

product that comprises allantoin, purified water, sweet almond oil, olive oil, rice bran oil, emulsifying wax, milk protein, aloe vera, vitamin E, glycerol caprylate, piroctone alamine and guar silk. Anecdotal reports by patients experiencing RISR and radiation oncologists in a number of Australian cancer centres suggest that this emulsion may be effective in promoting healing, comfort, and pain relief. This product is used in some Australian and New Zealand cancer centres in the management of RISR, however there has not been empirical evidence supporting this claim. This study investigated the effects of the NOCA compared to aqueous cream (which is the current standard of care at the study site) in patients with breast cancer/ lung cancer and head and neck cancer receiving radical radiotherapy.

METHODS AND MATERIALS

Participants in this double-blind randomised controlled trial were selected from patients receiving radical radiotherapy for lung, breast or head and neck cancer at the Royal Brisbane and Women's Hospital, a tertiary cancer care centre. All eligible patients were approached consecutively during Oct 2012 to April 2013. Patients over 18 years of age with definitive diagnosis of breast, lung and head and neck cancer, receiving radiotherapy (>50 Gy) either as primary treatment or post-operative treatment to their chest, breast/axilla or head and neck were eligible. Patients were excluded if they were unable to consent or had a pre-existing skin rash, ulceration or open wound in the treatment area. Patients were also excluded if they had a known skin allergy or other systemic skin disease (even if not directly affecting irradiated fields), any known allergic reaction to any ingredient of either the NOCA or the aqueous cream, failed patch test, or were not available for follow-up post-treatment. Eligible and consented patients were recruited into the study. Ethics was approved before commencement of the study by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/12/QBRW/90). Baseline characteristics were collected and clinical variables such as age, gender, ethnicity, stage of cancer, comorbidity,

prior and concurrent anti-cancer therapy, body mass index, smoking, cup-size (for patients with breast and axilla treated), daily dose (Gy/fraction), total dose to region of interest, radiation technique (external beam via Tomotherapy or 3D conformal RT) and boost treatment were recorded.

Patients were randomly allocated (1:1) to the intervention group to receive Cream 1 (NOCA), or Cream 2 (aqueous cream). Blocked randomisation was performed, with a block size of six, by a computer generated random number list prepared by an investigator who had no clinical involvement in the trial. This process concealed the sequence until interventions were assigned. Stratification by irradiated site: (1) breast, (2) lung or (3) head and neck, BMI categories: (1) underweight <18.50, (2) normal =18.50-24.99, (3) overweight =25-29.99, or (4) obese >30 and smoking status: (1) smoking, or (2) non-smoking defined the 24 strata. After patient consent was obtained, the research nurse then randomised participants to either receive Cream 1, or receive Cream 2 according to the generated blocking sequence. Blinding was accomplished by not disclosing to the research nurse, medical officers, radiation therapists, nurses or participants which preparation was used. Both topical preparations (Cream 1 and Cream 2) were white in colour, had similar consistency, and did not have a distinct odour. Both topical preparations were provided and coded as Cream 1 or Cream 2 by the manufacturer in identical tube containers. The manufacturer only disclosed the cream coded at the completion of data collection.

Patients were instructed to commence applying a thin layer of their allocated cream on the area of skin being irradiated at the onset of radiotherapy, twice a day or more as needed depending on the occurrence of RISR and pain, until the skin reaction subsided. The protocol did not specify the time of day for cream application. If moist desquamation occurred, the topical preparation was discontinued in the area of skin breakdown and dressings were applied until the wound healed as per standard care. Patients were asked to continue to apply the topical preparation onto the irradiated area that displayed no

breakdown. All participants were given written instructions on how to apply the allocated treatment (see Appendix 1). All other skin care advice given to both groups of patients were the same, as per the local policy of the Royal Brisbane and Women's Hospital (see Appendix 2). Baseline and weekly scores during treatment were collected when patients attended the radiation oncology department. At completion of radiotherapy, the research nurse contacted the patient via telephone over the four weeks post-treatment. Data collection was undertaken on the same day as much as possible, however, this was not always possible due to logistical challenges.

Severity of RISR was the primary outcome and was measured using The Common Toxicity Criteria for Adverse Events (CTCAE- Version 4.0) (14). This instrument is commonly used and well validated in radiation oncology for assessing radiation dermatitis (15). The assessment was undertaken on the worst toxicity present within the treatment field by a research nurse with extensive clinical experience in radiation oncology during their review. We assessed the inter-rater reliability by randomly examining the independent assessments of skin toxicity scores for 20 patients, evaluated by the nurse and the treating medical staff during the last week of treatment. The intra-class correlation coefficient was one, representing absolute agreement. The secondary outcomes were skin-related quality of life, pain, itching, and other cream usage. Skindex-16 was used to measure the effects of skin condition on quality of life (16, 17). This tool is a reliable and valid self-administered survey comprising 16 items in three scales to assess patient emotion, symptoms and functioning. Item responses are standardized from 0 (no effect) to 100 (maximal effect). Permission to use this tool was granted by the author. We also measured pain using the worst pain item of the Brief Pain Inventory (BPI) from the preceding seven days (18). The participant was asked to rate their pain level at the irradiated area. The BPI was selected because it was an easy tool to assess pain and has been well validated in both the clinical and research settings in cancer care. The scale of 0 to 10 is simple for patients to use and reflects common clinical assessment of pain. We considered 1-3 as mild pain, 4-6 as

moderate pain and 7-10 as severe pain. Itching was scored on a numeric analogue scale of 0-10 in the treated skin (0= no itching at all), (10= itching as bad as you can imagine). We considered 1-3 as mild itching, 4-6 as moderate itching and 7-10 as severe itching. Treatment interruptions due to severe skin reactions were documented throughout the study (Yes/No). This decision was determined by the treating radiation oncologist. Adverse events included any allergic reactions from the allocated treatment, and were reported by investigators using the CTCAE v4 (14). In addition, trial treatment compliance and use of other topical treatment was also documented.

A sample size of at least 81 in each arm was required to detect a 20% difference in Grade 2 or more skin reactions using a 2-sided significance test ($\alpha=0.05$) with a power of 80%. A 20% difference was considered clinically significant. Assuming that approximately 5% of patients could drop out of the study; an additional 5 patients in each arm were added in the final sample size.

Intention-to-treat analyses were carried out. Patient characteristics between arms were compared using the chi-square test for discrete variables and the t-test for continuous variables. Acute reactions were evaluated using Kaplan-Meier actuarial plots (time-to-event curves) with the log-rank test used to determine significant difference between arms. The proportion of patients exhibiting a specified toxicity at a given time were plotted as prevalence plots, with 95% confidence intervals to show severity and duration of reactions. Univariate logistic regression models were used to determine the significance of factors ($\alpha\leq 0.05$) to be included in the multivariate logistic regression model. A generalized linear interactive modelling package (GLIM4) was used to analyse the data.

RESULTS

A total of 174 patients were randomised and completed planned radiation therapy and assessment. Eighty-nine participants received Cream 1 and 85 received Cream 2. Participant and treatment characteristics are listed in Table 1. All patients completed

radiation treatment as planned excepted for one patient in the Cream 1 group (See Fig 1). There was no statistically significant difference in participants' characteristics when considering age, gender, ethnicity, treatment site, smoking status, body mass index, breast cup size (only for breast cancer patients), concurrent anti-cancer therapy, dose (Gy), fractions and boost application.

Insert Table 1 and Figure 1 about here

CTCAE Skin Toxicity

Overall, patients who received Cream 1 had a significantly lower average level of skin toxicity at week 3 ($p<0.05$), but had statistically higher average levels of skin toxicity at weeks 7, 8, and 9 (all $p<0.001$) (see Fig 2). When investigating skin toxicity by grades, there was a significantly higher proportion of patients developing Grade 1 or more skin toxicity in patients receiving Cream 2 at week 3 ($p=0.02$). However, there were significantly higher proportions of patients developing Grade 1 or more skin toxicity in patients receiving Cream 1 at weeks 6 ($p=0.048$) and 8 ($p=0.009$). There were higher proportions of patients developing Grade 2 or more skin toxicity in the Cream 1 group compared to the Cream 2 group at weeks 6 ($p=0.045$), 7 ($p<0.001$), 8 ($p=0.02$) and 9 ($p=0.001$) (See Fig 3). There were no significant differences in the time-to-event data when examining the incidence of Grade 2 or more skin toxicity ($p=0.82$) (see Suppl 3) and Grade 3 or more skin toxicity ($p=0.85$) (see Suppl 4). There was no association between cup size (A,B,C vs D, E, F and G) and incidence of Grade 2 or more skin toxicity ($p=0.63$) in the sub-group analysis of patients having their breast or axilla treated ($n=89$).

Insert Figures 2 and 3 about here

Pain, itching, skin-related quality of life and other cream usage

In regards to pain measured as worst pain over the past 7 days ranging from 0-10, patients in the Cream 2 group had a significantly higher average level of worst pain compared to the Cream 1 group at week 3 ($p<0.05$), but not at other weeks (see Suppl 5). Similarly, when we examined worst pain by severity, a significantly higher proportion of patients in the Cream 2 group experienced (moderate or more) worst pain compared to the Cream 1 group at week 3 ($p=0.03$). However, at later weeks, higher percentages of patients in the Cream 1 group developed (severe) worst pain at week 4 ($p=0.04$), and (weak or more) worst pain at week 6 ($p=0.04$) and week 7 ($p<0.001$).

In terms of itching, patients in the Cream 2 group had a significantly higher level of itching compared to those in the Cream 1 group at week 3 ($p<0.05$). However, when the severity of itching was examined (moderate or more), we did not observe any difference. There were no differences in skin-related quality of life scores at any week with all $p>0.05$ and in participants' need for any dressing ($p=0.45$) throughout all time points between groups. There were no adverse effects reported in either group. However, a significantly higher proportion of participants in the Cream 1 group used a range of other topical treatments in addition to the allocated cream to manage their skin toxicity other than the trial cream at weeks 8 ($p=0.049$) and 9 ($p=0.01$) (see Suppl 6).

Among those who developed skin toxicity as measured by CTCAE Grade 2 or more ($n=148$), there was no difference in pain and itching between the Cream 1 group and the Cream 2 group with all $p>0.05$. Among those who developed CTCAE Grade 3 or more ($n=27$), there was a significant difference in mild itching, but not in any other categories of itching or pain (see Table 2).

Insert Table 2 about here.

Univariate and multivariate Analysis

A logistic regression model examined the association between factors (including treatment arm and demographic/clinical characteristics) and the binary dependent variable (CTCAE Grade 2 or more) skin toxicity. At the univariate level, skin toxicity was associated with age ($p=0.04$), treatment site (breast vs lung) ($p<0.001$), and boost application ($p<0.001$). These variables were subsequently fitted to the multivariate regression model. The treatment site (lung) was found to be a significant independent predictive factor for Grade 2 or more skin toxicity ($p<0.001$) (See Table 3). There was a strong trend for Cream 2 to reduce the incidence of grade 2 or more skin toxicity in comparison to Cream 1 ($p=0.056$).

Insert Table 3 about here

DISCUSSION

Over the years, there have been technologic advances in radiation treatment (19, 20), however skin reactions remain a prevalent issue facing this patient population. The results of this study suggest that over half of all participants developed Grade 2 or more skin toxicity and approximately 16% of participants developed a Grade 3 skin toxicity sometime during their treatment. A systematic review undertaken by our team suggested that the most potentially effective treatment may be systemic oral enzymes and that no single treatment is superior to other treatments in preventing and managing radiation skin reactions (10). Despite this, topical treatments remain a key area of skin care practice, with the literature reporting a range of products being used around the world (10, 21).

This study was originally designed due to anecdotal reports from patients and healthcare professionals suggesting the potential efficacy of the NOCA. The results of our study indicate that this oil-based natural emollient is not superior to the usual practice (aqueous cream) in our cancer care centre. The results of this study report that the outcomes

of both topical interventions are quite similar. The NOCA appears to be more effective (though not significantly) for managing skin toxicity compared to aqueous cream up to week 5, however, it becomes less effective at later weeks into the treatment and beyond radiation treatment completion (week 6 and beyond). This group of patients also used more topical treatment other than the allocated treatment. However, there were no major differences in pain, itching and skin-related quality of life between the two groups. In light of these results, clinicians and patients can base their decision on costs and preferences. We are hesitant to recommend the use of both creams during radiation treatment (i.e. the NOCA from week 0 to week 5, then the aqueous cream thereafter). Because this approach is not yet tested and can be confusing to patients especially if they develop Grade 2 or more skin toxicity and requiring dressings.

There have been recent clinical studies suggesting the potential detrimental effects of aqueous cream on healthy individuals (22) or those with previous history of atopic dermatitis (23). There has also been a suggestion that aqueous cream contains sodium lauryl sulphate and has not been designed to be a leave-on emollient, therefore should not be used for managing RISR (24). To the best of our knowledge, there has been no randomised controlled trial reporting detrimental effects for patients experiencing RISR. Despite these concerns, a recent UK survey study also confirmed that aqueous cream is a popular choice for treating RISR (21). Aqueous cream is commonly used possibly because of its potential benefits and low cost. The result of this study favouring aqueous cream is consistent with findings from our previous RCT. In 2002, a Phase III non-blinded RCT conducted by our research team reported that aqueous cream was more useful for reducing dry desquamation and pain related RISR compared to aloe vera gel (25). A recent RCT conducted in 2013 suggested no difference in outcomes between those who received calendula cream and aqueous cream for managing RISR (26). The current study reports that aqueous cream is superior to the NOCA in terms of severity of skin toxicity at least at certain weeks. Given the positive results of aqueous cream in comparison with an emollient, it is reasonable to

speculate that the barrier function of the paraffin oil in the aqueous cream might be advantageous for patients with RISR. Given a number of barrier topical interventions are now available, future trials can investigate the results across different types of barrier treatments for managing RISR.

In this study, we were not able to measure skin dose, which is a limitation of this study. In spite of this, we are confident of our results. Overall, this is a suitably powered, rigorously designed randomised controlled trial. The two groups were extremely well balanced and comparable based on the similar demographic and clinical/treatment characteristics listed in Table 1. These findings indicate a successful stratified and blocked randomisation. In addition, the intra-class correlation coefficient of “1” suggested high inter-rater reliability of the trial. Due to ethical concerns of limiting patients to use other skin treatments, the study design allowed the use of other topical treatment as prescribed by their medical officers. Despite this, we have conducted intention-to-treat analysis. We believe that the finding that one group had to use significantly more of other cream was a significant finding in itself.

Despite the high number of randomised controlled trials in the management of RISR, the evidence base is limited with a very low number of studies investigating the same interventions (10). This study adds to the literature to inform health professionals and patients of the efficacy of a NOCA commonly used in Australian cancer care centres in comparison to another commonly used topical intervention in patients experiencing RISR. Future research should continue to identify the best topical regimen for this important clinical problem.

References

1. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer*. 2005 Sep 15;104(6):1129-37. PubMed PMID: 16080176. Epub 2005/08/05. eng.
2. Sitton E. Early and late radiation-induced skin alterations. Part I: Mechanisms of skin changes. *Oncol Nurs Forum*. 1992 Jun;19(5):801-7. PubMed PMID: 1608843. Epub 1992/06/01. eng.
3. Porock D. Factors influencing the severity of radiation skin and oral mucosal reactions: development of a conceptual framework. *Eur J Cancer Care*. 2002 Mar;11(1):33-43. PubMed PMID: 11966833. eng.
4. Naylor W, Mallett J. Management of acute radiotherapy induced skin reactions: A literature review. *Eur J Oncol Nurs*. 2001;5(4):221-3.
5. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol*. 2006 Jan;54(1):28-46. PubMed PMID: 16384753. Epub 2005/12/31. eng.
6. Maduro JH, Pras E, Willemse PH, de Vries EG. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. *Cancer Treat Rev*. 2003 Dec;29(6):471-88. PubMed PMID: 14585258. eng.
7. McQuestion M. Evidence-Based Skin Care Management in Radiation Therapy: Clinical Update. *Sem Oncol Nursing*. 2011;27(2):e1-e17.
8. Noble-Adams R. Radiation-induced reactions 1: an examination of the phenomenon. *Br J Nurs*. 1999;8(17):1134-40.
9. Bolderston A, Lloyd NS, Wong RK, Holden L, Robb-Blenderman L. The prevention and management of acute skin reactions related to radiation therapy: a systematic review and practice guideline. *Support Care Cancer*. 2006 Aug;14(8):802-17. PubMed PMID: 16758176. Epub 2006/06/08. eng.
10. Chan R, Webster J, Chung B, Marquart L, Ahmed M, Garantziotis S. Interventions for preventing and managing radiation-induced skin reactions in patients with cancer: a systematic review and meta-analysis. *BMC Cancer*. 2014;14:53.
11. De Ruyck K, Van Eijkeren M, Claes K, et al. Radiation-induced damage to normal tissues after radiotherapy in patients treated for gynecologic tumors: association with single nucleotide polymorphisms in XRCC1, XRCC3, and OGG1 genes and in vitro chromosomal radiosensitivity in lymphocytes. *Int J Radiation Oncol Biol Phys*. 2005 Jul 15;62(4):1140-9. PubMed PMID: 15990020. eng.
12. Glean E, Edwards S, Faithfull S, et al. Intervention for acute radiotherapy induced skin reactions in cancer patients: the development of a clinical guideline recommended for use by the college of radiographers. *J Radiother Pract*. 2001;2:75-84.
13. Chan R, Larsen E, Chan P. Re-examining the evidence in Radio-dermatitis Management Literature: An overview and critical appraisal of Systematic Reviews. *Int J Radiation Oncol Biol Phys*. 2012;e358.
14. National Cancer Institute. Common Terminology Criteria for Adverse Events (Version 4). National Cancer Institute, National Institutes of Health; 2009.
15. Langendijk JA, Oosting SF. Grading system and management guidelines for dermatitis induced by head and neck radiotherapy plus cetuximab: clinical validation required. *Ann Oncol*. 2011 Oct;22(10):2157-9. PubMed PMID: 21878428. Epub 2011/09/01. eng.
16. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *J Invest Dermatol*. 1996 Nov;107(5):707-13. PubMed PMID: 8875954. Epub 1996/11/01. eng.

17. Chren MM, Lasek RJ, Sahay AP, Sands LP. Measurement properties of Skindex-16: a brief quality-of-life measure for patients with skin diseases. *J Cutan Med Surg*. 2001 Mar-Apr;5(2):105-10. PubMed PMID: 11443481. Epub 2001/07/10. eng.
18. Cleeland C. Measurement of pain by subjective report. In: Chapman C, Loeser J, editors. *Advances in Pain Research and Therapy*. 12. New York: Raven Press; 1989. p. 391-403.
19. Freedman GM, Li T, Nicolaou N, Chen Y, Ma CC, Anderson PR. Breast intensity-modulated radiation therapy reduces time spent with acute dermatitis for women of all breast sizes during radiation. *Int J Radiation Oncol Biol Phys*. 2009 Jul 1;74(3):689-94. PubMed PMID: 19362779. Pubmed Central PMCID: 2720600.
20. Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008 May 1;26(13):2085-92. PubMed PMID: 18285602.
21. Harris R, Probst H, Beardmore C, et al. Radiotherapy skin care: A survey of practice in the UK. *Radiography*. 2012;18(1):21-7.
22. Mohammed D, Matts PJ, Hadgraft J, Lane ME. Influence of Aqueous Cream BP on corneocyte size, maturity, skin protease activity, protein content and transepidermal water loss. *The British journal of dermatology*. 2011 Jun;164(6):1304-10. PubMed PMID: 21443526.
23. Danby SG, Al-Enezi T, Sultan A, Chittock J, Kennedy K, Cork MJ. The effect of aqueous cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis. *The British journal of dermatology*. 2011 Aug;165(2):329-34. PubMed PMID: 21564067.
24. Patel AN, Varma S, Batchelor JM, Lawton PA. Why aqueous cream should not be used in radiotherapy-induced skin reactions. *Clinical oncology*. 2013 Apr;25(4):272. PubMed PMID: 23302394.
25. Heggie S, Bryant GP, Tripcony L, et al. A Phase III study on the efficacy of topical aloe vera gel on irradiated breast tissue. *Cancer Nurs*. 2002 Dec;25(6):442-51. PubMed PMID: 12464836. Epub 2002/12/05. eng.
26. Sharp L, Finnila K, Johansson H, Abrahamsson M, Hatschek T, Bergenmar M. No differences between Calendula cream and aqueous cream in the prevention of acute radiation skin reactions--results from a randomised blinded trial. *Eur J Oncol Nurs*. 2013 Aug;17(4):429-35. PubMed PMID: 23245940.

Figure 1. CONSORT Participant Flow Diagram

Figure 2. CTCAE Skin Toxicity (0-4) between group

Figure 3. CTCAE Skin Toxicity (2 or more) between group